

091936764

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
13 September 2001 (13.09.2001)

PCT

(10) International Publication Number  
**WO 01/65994 A3**(51) International Patent Classification<sup>7</sup>: C07H 21/04,  
C12P 19/34, C12Q 1/48, 1/68, G01N 27/26

(21) International Application Number: PCT/IL01/00212

(22) International Filing Date: 6 March 2001 (06.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
09/519,673 6 March 2000 (06.03.2000) US(71) Applicant (for all designated States except US): **TECH-  
NION RESEARCH AND DEVELOPMENT FOUN-  
DATION LTD.** [IL/IL]; Gutwirth Science Park, Technion  
City, 32000 Haifa (IL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ASSARAF, Yehuda**  
[IL/IL]; Kfar Kehilati, Rakefet, 20175 Doar Na Misgav  
(IL). **DRORI, Statvit** [IL/IL]; Tchernichovski Street 55,  
35704 Haifa (IL).(74) Agent: **G. E. EHRLICH (1995) LTD.**; Bezalel Street 28,  
52521 Ramat Gan (IL).(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,  
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,  
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,  
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,  
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**Published:**

— with international search report

(88) Date of publication of the international search report:

17 January 2002

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.(54) Title: METHOD OF AND KIT FOR ASSESSING RESPONSIVENESS OF CANCER PATIENTS TO ANTIFOLATE  
CHEMOTHERAPY(57) Abstract: A method for the assessment of the responsiveness of a cancer patient to antifolate-containing chemotherapy, the  
method is effected by searching for a mutation or mutations in a reduced folate carrier (RFC) gene in cells derived from the patient.

WO 01/65994 A3

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL01/00212

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04; C12P 19/34; C12Q 1/48, 1/68; G01N 27/26

US CL : 204/450; 435/6, 15, 91.2; 535/24.31, 24.33, 23.5

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 204/450; 435/6, 15, 91.2; 535/24.31, 24.33, 23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	GUO, W et al. Mechanisms of methotrexate resistance in osteosarcoma. Clinical Cancer Research. MARCH 1999, vol. 5, pp. 621-627; see entire document, but especially page 21, column 2 and page 624, Table 3.	1, 4, 12-14, and 23 ----- 1, 3-6, and 10-35
X --- Y	JANSEN, G, et al. A structurally altered human reduced folate carrier with increased folic acid transport mediates a novel mechanism of antifolate resistance. Journal of Biological Chemistry. 13 November 1998, Vol. 273, No. 46, pp. 30189-30198; see entire document, but especially page 30190, column 1, page 30191, column 1, and page 30194,	1, 4, 10-14, and 16-23 ----- 1, 3-6, and 10-35
Y	ROY, K, et al. A single amino acid difference within the folate transporter encoded by the murine RFC-1 gene selectively alters its interaction with folate analogues. Journal of	1, 5, 6, and 10-35
Y	TAKEMURA, Y, et al. Biological activity and intracellular metabolism of ZD1694 in human leukemia cell lines with different resistance mechanisms to antifolate drugs. Japanese Journal of Cancer Research. July 1996, vol. 87, pp. 773-780; especially page 773, columns 1-2.	1, 3-6, and 10-35



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

18 July 2001 (18.07.2001)

Date of mailing of the international search report

28 AUG 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

Box PCT

Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

TERRY J. DEY

Stephen L. Rawlings, Ph.D.

PARALEGAL SPECIALIST

Telephone No. (703) 3081600

TECHNOLOGY CENTER 1600

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL01/00212

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 2 and 7-9  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Enter reason
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL01/00212

### **C ntinuation of B. FIELDS SEARCHED Item 3:**

MEDLINE, CANCERLIT, BIOSIS, EMBASE, USPATFULL: reduced folate carrier-1 (RFC-1) gene, DHFR, FPGS, GARTF, TS, MDR1, MRP1, mutation, familial predisposition, cancer, leukemia, folate transport, methotrexate resistance, antifolate therapy, responsiveness, resistance, susceptibility, SSCP, PCR, sequencing